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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,638	01/22/2002	Robert P. Ryall	01-059-A	9398

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EXAMINER

DEVI. SARVAMANGALA J N

ART UNIT	PAPER NUMBER
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1645

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/054,638

Applicant(s)

RYALL, ROBERT P.

Examiner

S. Devi, Ph.D.

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-36, 46, 48-51, 56 and 57 ~~is/are~~ are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-36, 46, 48-51, 56 and 57 ~~is/are~~ are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

RESPONSE TO APPLICANT'S AMENDMENT

Applicant's Amendments

- 1) Acknowledgment is made of Applicant's amendments filed 04/03/06 and 12/18/06 in response to the non-final Office Action mailed 10/03/05. The latter is compliant under 37 CFR 1.121.

Status of Claims

- 2) Claims 52 and 54 have been canceled via the amendment filed 12/18/06.
Claims 18, 22-33, 35, 46, 48-51 and 57 have been amended via the amendment filed 12/18/06.
Claims 18-36, 46, 48-51, 56 and 57 are pending and are under examination.

Prior Citation of Title 35 Sections

- 3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

- 4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Maintained

- 5) The objection to the specification made in paragraph 5 Office Action mailed 10/03/05 under 35 U.S.C. § 132 as introducing new matter is maintained for reasons set forth therein.

Applicant states that he has removed the terms 'saponin adjuvant' and 'QG-21' from the pending claim 35. Applicant contends that his amendment does not constitute new matter since an applicant is allowed under the authority of 37 CFR § 1.57(d) and 1.57(b) to incorporate by reference non-essential material. Applicant submits that paragraph 22 of the specification specifically reserved the right to incorporate by reference essential and nonessential material, by material pursuant to 37 CFR § 1.57(b). Applicant states that the originally filed specification in paragraph 33 clearly directed skilled artisans to Powell and Newman's text wherein Chapter 20 entitled *Water-soluble Phosphazene Polymers for Parental and Mucosal Vaccine Delivery*, pp. 473-493 is directed

to describing the chemistry and biological activity of phosphazens notably including PCPP (poly[di(carboxyphosphoryl)phosphazene]) and PCGPP. Applicant directs the Office to see page 476 of Powell and Newman. Applicant cites case law and submits that providing commonly known chemical names in an amendment to the specification for the compounds associated with the acronym 'pcpp' adjuvant is analogous to the permissible action deemed by the Federal Circuit to be merely renaming of an otherwise known and identified compound.

Applicant's arguments have been carefully considered, but are not persuasive. Applicant's removal of the terms 'saponin adjuvant' and 'QG-21' from the pending claim 35 has been noted. It should be noted that the new provisions in 37 CFR § 1.57(b)-(g) apply to applications filed on or after 21 October 2004. To be an effective incorporation by reference, a clear intent and identification must be expressly presented in the specification. The use of root words 'incorporate' and 'reference' is required. The 'referenced' publication must be clearly identified. 37 CFR § 1.57(b). In the instant case, the filing date of the instant application is 01/22/2002. The paragraph 22 of the originally filed instant specification is reproduced herein below which does not pertain to and does not describe 'adjuvants' now recited in claim 35:

[0022] Capsular polysaccharides can be prepared by standard techniques known to those of skill in the art (ref). In the present invention capsular polysaccharides prepared from serogroups A, C, W-135 and Y of *N. meningitidis* are preferred.

Likewise, the originally filed paragraph 33 of the instant specification is reproduced below which does not pertain to and does not describe 'adjuvants' now recited in claim 35:

[0033] The amount of vaccine of the invention to be administered a human or animal and the regime of administration can be determined in accordance with standard techniques well known to those of ordinary skill in the pharmaceutical and veterinary arts taking into consideration such factors as the particular antigen, the adjuvant (if present), the age, sex, weight, species and condition of the particular animal or patient, and the route of administration. In the present invention, the amount of polysaccharide-protein carrier to provide an efficacious dose for vaccination against *N. meningitidis* can be from between about 0.02 µg to about 5 µg per kg body weight. In a preferred composition and method of the present invention the dosage is between about 0.1 µg to 3 µg per kg of body weight. For example, an efficacious dosage will require less antibody if the post-infection time elapsed is less since there is less time for the bacteria to proliferate. In like manner an efficacious dosage will depend on the bacterial load at the time of diagnosis. Multiple injections administered over a period of days could be considered for therapeutic usage.

The two paragraphs, as originally filed, neither cite Powell and Newman's publication, nor use the root words 'incorporate' and 'reference' to incorporate Powell and Newman's publication by reference into the specification. Lastly, the reference of Powell and Newman has not even been submitted to the Office via PTO-1449 for the Office to verify that limitations in claim 35 such as

'DC-chol', 'pcpp' and 'CpG' indeed correspond to the now recited expanded limitations. This is important because, as set forth below in paragraph 31, the limitation 'oligodeoxynucleotide motifs' added to claim 35 does not appear to merely rename "CpG", because the art appears to refer to 'oligodeoxynucleotide motifs' by the abbreviation 'ODN' (see paragraph [0218] of US 20050208605). The objection stands.

Rejection(s) Moot

- 6) The rejection of claims 52 and 54 made in paragraph 17 of the Office Action mailed 12/07/04 and maintained in paragraph 45 of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is moot in light of Applicants' cancellation of the claims.
- 7) The rejection of claims 52 and 54 made in paragraph 26 of the Office Action mailed 12/07/04 and maintained in paragraph 49 of the Office Action mailed 10/03/05 under 35 U.S.C. § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992, already of record) and McMaster (6,146,902 - Applicants' IDS submitted 07/07/04) as modified by Andre *et al.* (*In: Modern Vaccinology*. (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, pp. 41-54, 1994, already of record), Levine *et al.* (*In: Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al.* Baltimore, USA, pages 228-230, November, 1997, already of record) and Lindberg AA (*Vaccine* 17: S28-S36, 1999 – Applicants' IDS) as applied to claim 51, 33 and 18 above, and further in view of Avendano *et al.* (*Pediatric Infect. Dis. J.* 12: 638-643, 1993), is moot in light of Applicants' cancellation of the claims.
- 8) The rejection of claims 52 and 54 made in paragraph 53(q) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicant's cancellation of the claims.

Rejection(s) Withdrawn

- 9) The rejection of claim 26 made in paragraph 20(h) of the Office Action mailed 12/07/04 and maintained in paragraph 42 of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.
- 10) The rejection of claims 49 and 50 made in paragraph 20(t) of the Office Action mailed 12/07/04 and maintained in paragraph 43 of the Office Action mailed 10/03/05 under 35 U.S.C. §

112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

11) The rejection of claim 48 made in paragraph 19 of the Office Action mailed 12/07/04 and maintained in paragraph 46 of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicant's amendment to the claim.

12) The rejection of claim 49 made in paragraph 51 of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicant's amendment to the claim.

13) The rejection of claims 46 and 48 made in paragraph 52 of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicant's amendment to the claims.

14) The rejection of claim 18 made in paragraph 53(a) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

15) The rejection of claim 22 made in paragraphs 53(b), 53(c), 53(d) and 53(f) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

16) The rejection of claim 35 made in paragraph 53(e) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

17) The rejection of claim 23 made in paragraph 53(g) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

18) The rejection of claims 24, 25, 27-29 and 33 made in paragraph 53(h) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

19) The rejection of claims 30-32 made in paragraph 53(j) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's

amendment to the claims.

20) The rejection of claim 35 made in paragraphs 53(k) and 53(l) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

21) The rejection of claim 51 made in paragraph 53(n) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

22) The rejection of claim 57 made in paragraph 53(o) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

23) The rejection of claims 46 and 48 made in paragraph 53(p) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

24) The rejection of claims 19-29, 33-35, 46, 48-51, 56 and 57 made in paragraph 53(q) of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the base claim(s).

Rejection(s) Maintained

25) The rejection of claim 19 made in paragraph 20(b) of the Office Action mailed 12/07/04 and maintained in paragraph 44 of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

26) The rejection of claims 18-33 and 51 made in paragraph 22 of the Office Action mailed 12/07/04 and maintained in paragraph 47 of the Office Action mailed 10/03/05 under 35 U.S.C. § 103(a) as being unpatentable over McMaster (6,146,902 – Applicants' IDS submitted 07/07/04) in view of Andre *et al.* (*In: Modern Vaccinology*, (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, pp. 41-54, 1994, already of record), Levine *et al.* (*In: Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al.* Baltimore, USA, pages 228-230, November, 1997, already of record) and Lindberg AA (*Vaccine* 17: S28-S36, 1999 – Applicants' IDS), is maintained for reasons set forth therein and herein below in the paragraph immediately below.

27) The rejection of claims 18-36, 46, 48-51, 56 and 57 made in paragraph 23 of the Office Action mailed 12/07/04 and maintained in paragraph 48 of the Office Action mailed 10/03/05 under 35 U.S.C § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992, already of record) and McMaster (6,146,902 – Applicants' IDS submitted 07/07/04) in view of Andre *et al.* (*In: Modern Vaccinology*, (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, pp. 41-54, 1994, already of record); Levine *et al.* (*In: Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al.* Baltimore, USA, pages 228-230, November, 1997, already of record) and Lindberg AA (*Vaccine* 17: S28-S36, 1999 – Applicants' IDS), is maintained for reasons set forth therein and herein below.

Applicant has addressed the two art rejections mentioned above together with one set of arguments.

Applicant submits the following arguments: (a) MPEP § 2143 describes three criteria that were collectively developed to prevent the impermissible use of hindsight during examination; some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; a reasonable expectation of success; and the prior art reference teaching or suggesting all of the claim limitations. The Office has not sufficiently provided the request objective evidence for establishing the *prima facie* case of obviousness. (b) It may have been obvious to try to develop Applicant's claimed compositions, however, this does not establish the objective evidence required for *prima facie* obviousness. (c) The Federal Circuit has repeatedly held that using an obvious to try rational is a legally impermissible basis for attempting to establish a motivation to combine references especially in unpredictable fields such as immunology and vaccinology. (d) When analyzing a patent claim for obviousness, the claim should be considered as a whole, but the differences between the claim and the prior art need to be identified to place the obviousness analysis into proper perspective. (e) The Applicant's remarks concerning the state of the art recognized by Granoff (WO 98/58670) are still relevant to the complete picture that the Office is required to consider when establishing the substantive evidence request for a *prima facie* conclusion of obviousness. The meningococcal serotype distribution and the disease occurrence at the time of the '670 publication make the omission of the Y and W-135 serogroups 'conspicuous and significant'. The '670 reference acknowledges the licensure of a tetravalent (A, C, Y and W-135) meningococcal polysaccharide vaccine composition. (f) It is well settled that before the purported

teachings of a reference can be considered for use in an obviousness rejection, the reference(s) itself must sufficiently teach one skilled in the art how to make and use the compositions and/or methods allegedly disclosed therein pursuant to § 112. The Federal Circuit in *Beckman Instruments, Inc. v. LKB Produkter AB* held that in order to render a claimed apparatus or method obvious under Section 103, the prior art must enable one skilled in the art to make and use the apparatus or method. (g) The Office continues to trivialize the unpredictability in the field of biologics and vaccines. Until the applicant's invention, it was not taught or suggested in the art that meningococcal Y and/or W-135 serogroup polysaccharide-protein conjugates could be combined without deleterious side effects or suppression of immunogenicity of any one or more, or potentially all of the respective meningococcal serogroup polysaccharide-protein carrier conjugates present in the composition. (h) A 1998 paper by Gizurason (Attachment A) describes a great number of adverse interactions and failed vaccine development attempts including a suppression in the immunogenicity of the measles vaccine upon an attempted combination of meningococcal polysaccharides A and C serogroups vaccines with a measles vaccine. Gizurason stated that the "meningococcal seroconversion was *unaffected*", but the immunogenicity of the measles vaccine was significantly depressed, and that the interactions may occur because of physical or chemical interactions within the vaccine formulation, interactions between live vaccines or immunological interference [Emphasis added]. (i) Those skilled in the vaccinal arts do not treat the difficulties and lack of predictability associated with vaccine conception, formulation, production, and administration with triviality. (j) Given the epidemiology of meningococcal disease and the meningococcal serotype distribution, one skilled in the art should be able to trivially produce a successful meningococcal serogroup B polysaccharide-carrier protein vaccine conjugate. However, the fact of the matter is that B serogroup conjugates have proven very difficult for those skilled in the art to produce. (j) Applicant acknowledges that meningococcal B serogroup polysaccharide-carrier protein conjugates have been developed, but alleges that these conjugates currently have only been developed for small scale relatively isolated and unique populations. (k) It may have been obvious to try to develop the Applicant's presently claimed compositions, however, this does not establish the objective evidence required for *prima facie* obviousness. The Federal Circuit has repeatedly held that using an obvious to try rationale is a legally impermissible basis for attempting to establish a motivation to combine references especially in unpredictable fields such as immunology and vaccinology.

Applicant's arguments have been carefully considered, but are not persuasive. Contrary to Applicant's assertion, the obviousness rejections of record are fully compliant with MPEP § 2143 in that suggestion or motivation to modify the reference or to combine reference teachings is either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art; there is a reasonable expectation of success; and the prior art reference(s) teach or suggest all of the claim limitations. The Office has clearly set forth a *prima facie* case of obviousness. No obvious to try rational has been used.

Applicant's remarks concerning the alleged state of the art recognized by Granoff (WO 98/58670) were fully addressed in the Office Action mailed 10/03/05. The Office Action documented how it is self-evident that despite Granoff's alleged 'conspicuous and significant' omission, McMaster did proceed to and succeed in making protein-capsular polysaccharide conjugates comprising purified meningococcal serogroups A, C, W-135 and Y capsular polysaccharides. The Office Action brought to Applicant's attention the fact that nothing in Granoff's disclosure (WO 98/58670) teaches not to combine the four separately made meningococcal capsular polysaccharide-protein conjugates of McMaster. The state of the art at the time of the instant invention as opposed to the state of the art at the time of the publication of the '670 publication is what is relevant to the discussion herein. McMaster disclosed the very technology to produce the protein-capsular polysaccharide conjugates comprising purified meningococcal serogroups A, C, W-135 and Y capsular polysaccharides. The *prima facie* evidence that Granoff's ('670) alleged teaching on the meningococcal serotype distribution and the disease occurrence at the time of the '670 publication did not deter, prevent, or discourage McMaster to develop and produce protein-capsular polysaccharide conjugates comprising purified meningococcal serogroups A, C, W-135 and Y capsular polysaccharides, did not deter, prevent, or discourage Lindberg to predict potential marketing of the meningococcal A + C + W135 + Y glycoconjugates, and did not deter, prevent, or discourage Levine *et al.* to perform a cost-effectiveness analysis for *routine immunization* with a quadrivalent A, C, Y and W-135 meningococcal polysaccharide-protein conjugate vaccine, is not a trivial matter. That no deleterious side effects or suppression of immunogenicity was expected by those skilled in the art and that a reasonable expectation of success of such a combined conjugate vaccine was anticipated by those of skill in the art at the time of the invention is evident from Levine *et al.* going to the extent of performing a cost-effectiveness analysis for routine immunization with a quadrivalent A,

C, Y and W-135 meningococcal polysaccharide-protein conjugate vaccine, and Lindberg predicting the potential marketing of the meningococcal A + C + W135 + Y glycoconjugates. The teachings of McMaster's patent when combined with the disclosure of Andre *et al.*, Levine *et al.*, and Lindberg AA as set forth, provide the *prima facie* evidence showing that the alleged 'obvious to try' rationale is baseless. The knowledge in the art at the time of the instant invention indicates that the concept of providing more than one capsular polysaccharide conjugates in one vaccine or one composition was not novel, but was well within the realm of routine experimentation since the art typically engaged in such experimentation. As set forth previously, at the time of the instant invention, Chong *et al.* (WO 99/42130) had already established reasonable expectation of success with a multivalent immunogenic molecule comprising multiple purified capsular polysaccharides or oligosaccharides of *Neisseria meningitidis* derived from serogroup A, C, W-135 and Y, each conjugated to a carrier protein for use as a medicament against meningitis. See claims 1, 6-8, 39 and 40; paragraph bridging pages 9 and 10; pages 10 and 12; and Examples 1, 2 and 4 of Chong *et al.* Costantino *et al.* had already evaluated combination meningococcal capsular polysaccharide- or oligosaccharide-protein conjugates for efficacy. Applicant has not addressed this objective evidence provided by the Office in support of the *prima facie* case of obviousness. Adding an additional art-known W-135 or Y conjugate such as McMaster's was well within the realm of what one of skill in the art usually engages in.

It is noted that conspicuously absent from Applicant's rebuttal is advancement of any argument with regard to the already art-known, separately made protein-capsular polysaccharide conjugates each comprising a purified capsular polysaccharide of meningococcal serogroup A, C, Y or W-135 as expressly taught by the primary reference of McMaster (US 6,146,902). It is well settled law that failure to consider the references together is inappropriate in view of the fact that the rejection was made under 35 U.S.C 103. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). *In re Young*, 56 CCPA 757, 403 F.2d 754, 159 USPQ 725 (1968). Contrary to Applicant's assertion, McMaster did provide detailed tables and protocols concerning meningococcal serogroup A, C, W-135 and Y capsular polysaccharide-protein conjugate vaccine production. At the time of the instant invention, the primary reference of McMaster already provided detailed teachings as to how to make the four individual meningococcal A, C, W-135 and Y capsular polysaccharide conjugates. McMaster was already successful in making individual protein-capsular polysaccharide conjugates comprising meningococcal serogroup W-135 or Y in addition to protein-

capsular polysaccharide conjugates of meningococcal serogroups A and C. Combining these conjugates as desired or as described to produce a combination immunological composition would require nothing more than routine experimentation given the explicit motivation to combine such conjugates. Lindberg had already predicted that meningococcal A + C + W135 + Y glycoconjugates will most likely be marketed (see thirds full paragraph in left column on page S34). Because a reasonable expectation of success of such a combined conjugate vaccine was anticipated by those of skill in the art at the time of the invention, Levine *et al.* went to the extent of performing a cost-effectiveness analysis for routine immunization with a quadrivalent A, C, Y and W-135 meningococcal polysaccharide-protein conjugate vaccine. These are clearly indicative of a reasonable expectation of success with a combination meningococcal A + C + W135 + Y glycoconjugate vaccine. Furthermore, as set forth previously, at the time of the instant invention, Chong *et al.* (WO 99/42130) had already established reasonable expectation of success with a multivalent immunogenic molecule comprising multiple purified capsular polysaccharides or oligosaccharides of *Neisseria meningitidis* derived from serogroup A, C, W-135 and Y, each conjugated to a carrier protein for use as a medicament against meningitis (see claims 1, 6-8, 39 and 40; paragraph bridging pages 9 and 10; pages 10 and 12; and Examples 1, 2 and 4). Nothing in the art at the time of the invention suggested a lack of reasonable expectation of success upon combining McMaster's individually produced meningococcal A, C, W135 and Y glycoconjugates as set forth in the rejection. Clearly, the Office has established a *prima facie* case of obviousness. A clear motivation to combine McMaster's individual conjugates, and a reasonable expectation of success are both found in the prior art teachings and/or in the knowledge generally available to one of ordinary skill in the art.

With regard to immunology and vaccinology allegedly being unpredictable fields and with regard to Applicant's remark on the 1998 reference of Gizurarson, the following must be noted. Gizurarson teaches how combining a viral vaccine that is not a conjugate vaccine, i.e., 'attenuated measles vaccine', with an *unconjugated* group A and group C meningococcal 'polysaccharide' vaccine did not affect the meningococcal seroconversion, but only depressed the immunogenicity of the attenuated measles vaccine. Instant claims however are not drawn to an immunological combination composition wherein two *unconjugated* meningococcal capsular polysaccharides are mixed with an 'attenuated' viral vaccine. In other words, the instant invention is unrelated to combining an attenuated viral vaccine with two *unconjugated* meningococcal capsular

polysaccharides to produce a combination composition. The instantly claimed composition is not a combined product of meningococcal conjugates and an attenuated viral vaccine either. Instead, the instant invention pertains to combining the already art-known or art-developed two, three, or four separately made conjugates of purified capsular polysaccharides of serogroups A, C, W-135 or Y wherein at least one serogroup is W-135 or Y.

The Applicant's remark that meningococcal B serogroup conjugates have proven very difficult for those skilled in the art to produce is not only incorrect, but is also misplaced. A review of the art on meningococcal capsular vaccines indicates that several immunogenic meningococcal serogroup B capsular polysaccharide-carrier protein conjugates have been successfully developed by those of skill in the art. To cite a few examples of US patents issued on immunogenic meningococcal serogroup B capsular polysaccharide-carrier protein conjugates: US 6,696,283; US 6,350,449; US 5,969,130; US 5,902,586; US 5,811,102 (already of record); US 5,773,007; US 5,683,699; US 5,576,002; US 4,727,136; US 6,638,513; and US 4,356,170. Whether or not meningococcal serogroup B polysaccharide-carrier protein conjugates have been developed allegedly only for small scale relatively isolated and unique populations is not an issue in the instant situation, since meningococcal serogroup B polysaccharide-carrier protein conjugate is not a requisite active element in the claimed composition.

With regard to Applicant's allegation of lack of suggestion in the prior art reference(s), the following should be noted. '[F]or the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references'. *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988). '[T]he question is whether there is something in the prior art as whole to suggest the desirability, and thus the obviousness, of making the combination'. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984). In the instant case, the cited references provide sufficient reason, desirability, suggestion, and/or motivation to combine their teachings. It is well-established that '[o]bviousness does not require absolute predictability of success'. *In re O'Farrell*, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Combining ingredients known to be useful for the same purpose to form a third composition, also useful for the same purpose, is considered obvious. Combining known substances for their expected result(s) and getting nothing more than the expected result is considered obvious. See *In re Kerkhoven* 626 F. 2d 846, 205 USPQ (CCPA 1980): "It is *prima facie* obvious to combine two compositions, each of which is

taught to form a third composition that is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-277, 126 USPQ 186, 188 (1960). As this court explained in *In re Crockett*, the idea of combining them flows logically from their having been individually taught in the prior art.”

In response to Applicant's remark on the alleged improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the rejection set forth is based on the prior art teachings and the knowledge which was within the level of ordinary skill at the time the claimed invention was made. Both the art rejections stand.

28) The rejection of claim 35 and those dependent therefrom made in paragraph 50 of the Office Action mailed 10/03/05 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is maintained for reasons set forth therein and herein below.

Applicant states that he has removed the limitation ‘saponin’ from the claim and corrected the limitation ‘QG-21’ to recite ‘QS-21’. Applicant submits that the claim terms “(N-2-Deoxy-2-L-leucylamino hydroacetate”, “(3-cholesterol)”, “Poly[bis(carboxylatophoxy)phosphazene] and/or Poly[di(carboxyatophoxy)phosphazene” were introduced partially in view of the Office’s previous indefiniteness rejection. Applicant states that the amendment to claim 35 was in part to recite the full terminology for the respective abbreviations known and recognized in the art for the instant subject matter set forth in the specification. Applicant concludes that the full terminology does not introduce new matter.

Applicant’s arguments have been carefully considered, but are not persuasive. First, the limitations mentioned above by Applicant, i.e., “(N-2-Deoxy-2-L-leucylamino hydroacetate” and “(3-cholesterol)” do not appear in the claim. Instead, the limitations “(N-2-Deoxy-2-L-leucylamino-β-D-glucopyranosyl)-N-octadecyldodecanoylamide hydroacetate” and “(3-β-[N-(N’,N’-demethylaminoethane)-carbamoyl]cholesterol)” are included in the claim. Second, the introduction of the brackets appears to exclude what is recited within the brackets. Third, the instant specification, as filed, does not provide support for these expanded limitations. Furthermore,

35) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

36) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.Mov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

37) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

March, 2007


S. DEVI, PH.D.
PRIMARY EXAMINER